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(54) **PROPHYLACTIC OR THERAPEUTIC AGENTS FOR DISEASES HAVING VASCULAR DYSFUNCTION ASSOCIATED WITH INSULIN RESISTANCE**

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(58) **Field of Search** 514/249

(56) References Cited

U.S. PATENT DOCUMENTS

4,665,182 A	5/1987	Nichol et al.
4,758,571 A	7/1988	Curtius et al.
4,774,244 A	9/1988	Curtius et al.
4,778,794 A	10/1988	Naruse et al.
5,753,656 A	5/1998	Sakai et al.

FOREIGN PATENT DOCUMENTS

EP	108890 A	5/1984
EP	209689 A	1/1987
JP	59-25323	2/1984
JP	59076086	4/1984
JP	61277618	12/1986
JP	267781/88	11/1988
JP	63267781	11/1988
JP	06 056669	3/1994

OTHER PUBLICATIONS

Walter et al., Inhalation Of The Nitric Oxide Synthase Cofactor Tetrahydrobiopterin In Volunteers. *Amer J. Respir & Crit Care Med.*, 1997, p 2009.

Wever et al., Tetrahydrobiopterin Regulates Superoxide And Nitric Oxide GENERATION Recombinant Endothelial Nitric Oxide Synthase, *Biochem Biophys Res*, 1997, pp 340-344.

Prast et al., Effects of Sepiapterin Treatment On Tetrahydrobiopterin Levels And Blood Pressure In Spontaneously Hypertensive Rats, *Biology of Nitric Oxide*, 1992, pp 10-12.

Pinkney et al, endothelial dysfunction:causes of the insulin resistance syndrome, *Diabetes Sep.* 1997, PS12.

Higashi et al. Relationship between insulin resistance and endothelium dependent vascular Relaxation in patients with essential hypertension, *Hypertension*, Jan. 1997, p 284.

Shinozaki et al., "Insulin Resistance . . .", *Circulation* 1995, vol. 92: p 1749-1757.

Shinozaki et al., "Demonstration of Insulin . . .", *Diabetes Care* 1996, vol. 19: p 1-7.

Shinozaki et al., "Role of Insulin Resistance . . .", *Stroke* 1996 vol. 27 p 37-43.

Shinozaki et al., "Insulin . . .", *Arterioscler, Thromb. Vasc.Biol.*, 1997 vol. 17: p 3302-3310.

Law et al., "Troglitazone Inhibits . . .", *J. Clin. Invest.* 1996, vol. 98: p 2546-2551.

Tardif et al., "Probucol and Multivitamins . . .", *N. Eng. J. Med.* 1997, vol. 337: p 365-372.

Hwang et al., "Fructose-Induced Insulin . . .", *Hypertension* 1987, vol. 10: p 512-516.

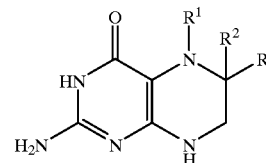
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(57) **ABSTRACT**

It is an object of the present invention to provide a pharmaceutical composition for effectively preventing or improving diseases having vascular dysfunction associated with insulin resistance. The present invention provides pharmaceutical compositions for preventing or treating diseases having vascular dysfunction associated with insulin resistance, comprising as an active ingredient a compound of the formula (I):



wherein R¹ and R² each represents a hydrogen atom or taken together with each other represent a single bond, while R³ represents —CH(OH)CH(OH)CH₃, —CH(OCOCH₃)CH(OCOCH₃)CH₃, —CH₃, —CH₂OH or a phenyl group when R¹ and R² each represents a hydrogen atom, or —COCH(OH)CH₃ when R¹ and R² together represents a single bond, or a pharmaceutically acceptable salt thereof.

9 Claims, No Drawings